Standardised mortality calculation for ischaemic heart disease/myocardial infarction. Figures are numbers for cohort unless stated otherwise

Age (years)	No of patients	Years of observation	No of deaths	No of deaths/year	Deaths/1000/ year in England (1998)	Expected No of deaths in cohort/year
15-24	15	0.55	0	0	0.003600	0.000054
25-34	145	0.51	0	0	0.028400	0.004118
35-44	473	0.49	0	0	0.222000	0.105006
45-54	1171	0.51	1.00	1.97	0.978100	1.145355
55-64	1583	0.50	5.00	10.00	3.277600	5.188440
65-74	1200	0.50	2.00	4.01	9.153800	10.984560
≥75	190	0.48	2.00	4.21	60.278400	11.452896
Not specified	824	0.49	N/A	N/A	N/A	N/A
Total	5601	0.50	10.00	20.20	73.941900	28.88

ischaemic heart disease, and chest pain. In patients who were taking sildenafil non-fatal events were angina (nine), chest pain (19), ischaemic heart disease (five), and myocardial infarction (seven) and fatal events were myocardial infarction (six) and ischaemic heart disease (four). One death was certified as congestive cardiac failure/ischaemic heart disease after intercourse. Four of the 10 patients who died were known to have had diabetes.

We used indirect standardisation to compare mortality from ischaemic heart disease (ICD-9 (international classification of diseases, 9th revision) codes 410-414) in the cohort with that in the general population of England in 1998 (table).[3] The standardised mortality ratio of 69.9 (95% confidence interval 42.7 to 108.0, based on Poisson error factors) indicates that the mortality in the cohort is 30.1% lower than that for English men in 1998, after adjustment for confounding effects of age.

Comment

The standardised mortality ratio indicates no evidence for a higher incidence of fatal myocardial infarction or ischaemic heart disease among men taking sildenafil. Underreporting of adverse events is possible, and bias caused by non-response among general practitioners and NHS restrictions on prescribing sildenafil cannot be excluded. The prevalence of diabetes in the cohort was 15%, which is similar to that (16%) in the manufacturer's clinical trials[4] but much higher than that in the general population (3.3% in men in England in 1998).[5] Though our results are reassuring it is inappropriate to accept these comparisons as definitive evidence of equivalence between this cohort of sildenafil users and men in the general population in England. This hypothesis needs to be examined by further clinical and pharmacoepidemiological research.

1 Arora RR, Timoney M, Melilli L. Acute myocardial infarction after use of sildenafil. *N Engl J Med* 1999;341:700.
2 Mann RD. Prescription-event monitoring—recent progress and future horizons. *Br J Clin Pharmacol* 1998;46:195-201.
3 Office for National Statistics. *Mortality statistics: general. Review of the registrar general on deaths in England and Wales, 1998.* London: Stationery Office, 2000.
4 Pfizer. *Viagra. Summary of product characteristics.* New York: Pfizer, 1998 (revised September 2000).
5 Bajekal M, Boerham R, Erens B, Falaschetti E, Hirani V, Primatesta P, et al. *Health Survey for England: cardiovascular disease '98. A survey carried out on behalf of the Department of Health.* London: Stationery Office, 1999.

Tsp509I polymorphism in exon 2 of the glucocorticoid receptor gene in relation to obesity and cortisol secretion: cohort study

Roland Rosmond, Claude Bouchard, Per Björntorp

Editorial by Sørensen and Echwald

Pennington Biomedical Research Center, Louisiana State University, Baton Rouge, LA 70808, USA
Roland Rosmond *postdoctoral researcher*
Claude Bouchard *executive director*

Chronically elevated cortisol levels can increase body fat, as seen clearly in Cushing's syndrome. Subjects with abdominal obesity share many of the hormonal, metabolic, and circulatory characteristics of people with Cushing's syndrome. A dysfunctional glucocorticoid receptor may add to the adverse health effects of excessive cortisol concentrations.

An Asn363Ser polymorphism in exon 2 of the glucocorticoid receptor gene (GRL) might be associated with overweight and an increased sensitivity to exogenous glucocorticoids.[1] We therefore examined whether this variant was associated with altered sensitivity to glucocorticoids as well as obesity with its related metabolic and haemodynamic abnormalities in a cohort of Swedish men.[2]

Participants, methods, and results

Subjects (a total of 284 men) were randomly selected from a larger cohort of men born in Gothenburg, Sweden, in 1944. The design of the study has been described elsewhere.[3] Measurements reported here were carried out in Gothenburg during 1995. All men gave written informed consent before participating in the study, which was approved by the local ethics committee.

Anthropometric measurements included body mass index, waist to hip ratio, and abdominal sagittal diameter. Salivary cortisol was measured repeatedly during an ordinary working day that had been selected at random. In addition, an overnight low dose (0.5 mg)

dexamethasone suppression test was performed at home and the difference in the salivary cortisol concentration before and after dexamethasone intake was calculated.[3] Endocrine measurements, other than cortisol, included testosterone, insulin-like growth factor I, and leptin, as described previously.[3] The following were measured in the overnight fasting state: insulin, glucose, triglycerides; total, high, and low density lipoprotein cholesterol; systolic and diastolic blood pressures; and heart rate.

Genotyping was performed on leucocyte DNA. Polymerase chain reaction amplification of the exon 2 of GRL was done using primers described previously,[4] and the products were digested with Tsp509I, which disclosed two genotypes—Asn363Asn and Asn363Ser.

The table shows the results for the two genotypes of GRL (table). There were 25 heterozygotes. The two groups of genotypes had similar anthropometry and endocrine, metabolic, and haemodynamic variables.

Comment

Our study shows that a point variation from ATT to GTT in exon 2 of GRL, resulting in a change from asparagine to serine at codon 363, is not associated with an altered sensitivity to glucocorticoids or with obesity and its related metabolic and haemodynamic perturbations. The frequency of the rare allele was 0.05 in our cohort, which is comparable to previous reports (0.07 and 0.03).[1 2]

The Ser363 variant is not associated with variables indicative of resistance to glucocorticoids.[4] In addition, at baseline examination in a previous report, the body mass index was not significantly higher in carriers of Ser363.[2] These findings are similar to those reported here.

The disparity between our study and previous work might reflect differences in genetic background or a different degree of linkage in the populations because the Asn363Ser polymorphism might serve as a marker for a yet unidentified functional variant.[1] We have recently shown that a BclI polymorphism in intron 1 of GRL was associated with decreased sensitivity to raised postprandial secretion of cortisol and several cardiovascular risk factors.[5] Consequently, we investigated the potential effects of interaction between Tsp509I and the BclI marker and showed that the BclI intronic mutation does not interact with the Ser363 variant for any of the phenotypes under study.

We conclude that GRL has several different polymorphisms and mutations, but that few of these are consistently associated with obesity and subtle physiological alterations in the hypothalamic-pituitary-adrenal axis regulating cortisol secretion. The Asn363Ser polymorphism does not seem to be one of the variants associated with such changes.

We thank Monique Chagnon, laboratory coordinator at Pennington Biomedical Research Center, for preparing and supervising the genotyping.

Contributors: RR did the genotyping, collected and analysed data, planned and designed the study, wrote the paper, and is the guarantor. CB discussed the core idea and participated in data interpretation and writing the paper. PB, principal investigator for the study of men born in 1944, participated in data interpretation and writing the paper.

Differences in anthropometric, endocrine, metabolic, and haemodynamic measurements by genotype of the GRL polymorphism. The confidence interval is for the mean difference; values are given as mean (SD)

| | Genotype | | |
	Asn363Asn (n=243)	Asn363Ser (n=25)	95% CI
Body mass index (kg/m^2)	26.2 (3.9)	26.0 (3.8)	−1.8 to 1.4
Waist circumference (cm)	95.4 (11.4)	93.8 (11.8)	−6.4 to 3.1
Waist to hip ratio	0.94 (0.07)	0.93 (0.08)	−0.04 to 0.02
Abdominal sagittal diameter (cm)	22.7 (3.7)	22.1 (3.4)	−2.1 to 0.9
Total salivary cortisol level (nmol/l)	7.5 (3.9)	7.1 (1.7)	−2.1 to 1.3
Dexamethasone suppression test (nmol/l)	12.0 (5.4)	11.9 (4.5)	−2.5 to 2.3
Testosterone (nmol/l)	19.7 (5.3)	19.6 (6.7)	−2.9 to 2.8
Insulin-like growth factor I (µg/l)	205.5 (65.0)	206.1 (66.1)	−26.3 to 27.5
Leptin (µg/l)	6.2 (4.4)	5.2 (3.5)	−2.8 to 0.8
Fasting insulin (mU/l)	12.5 (9.7)	13.7 (19.4)	−3.4 to 5.7
Fasting glucose (mmol/l)	4.6 (1.0)	4.3 (0.7)	−0.7 to 0.1
Triglycerides (mmol/l)	1.8 (1.0)	2.1 (1.4)	−0.2 to 0.7
Total cholesterol (mmol/l)	6.1 (1.0)	6.4 (1.3)	−0.2 to 0.7
High density lipoprotein cholesterol (mmol/l)	1.3 (0.3)	1.2 (0.3)	−0.2 to 0.1
Low density lipoprotein cholesterol (mmol/l)	4.1 (1.0)	4.2 (1.1)	−0.3 to 0.6
Systolic blood pressure (mm Hg)	129.9 (17.7)	125.1 (15.0)	−12.0 to 2.4
Diastolic blood pressure (mm Hg)	83.7 (10.6)	81.7 (9.3)	−6.3 to 2.3
Heart rate (beats/min)	68.9 (10.6)	68.5 (9.3)	−4.8 to 4.0

1 Lin RC, Wang WY, Morris BJ. High penetrance, overweight, and glucocorticoid receptor variant: case-control study. *BMJ* 1999;319:1337-8.
2 Huizenga NA, Koper JW, De Lange P, Pols HA, Stolk RP, Burger H, et al. A polymorphism in the glucocorticoid receptor gene may be associated with an increased sensitivity to glucocorticoids in vivo. *J Clin Endocrinol Metab* 1998;83:144-51.
3 Rosmond R, Dallman MF, Björntorp P. Stress-related cortisol secretion in men: relationships with abdominal obesity and endocrine, metabolic and hemodynamic abnormalities. *J Clin Endocrinol Metab* 1998;83:1853-9.
4 Koper JW, Stolk RP, de Lange P, Huizenga NA, Molijn GJ, Pols HA, et al. Lack of association between five polymorphisms in the human glucocorticoid receptor gene and glucocorticoid resistance. *Hum Genet* 1997;99:663-8.
5 Rosmond R, Chagnon YC, Holm G, Chagnon M, Pérusse L, Lindell K, et al. A glucocorticoid receptor gene marker is associated with abdominal obesity, leptin, and dysregulation of the hypothalamic-pituitary-adrenal axis. *Obes Res* 2000;8:211-8

(Accepted 18 September 2000)

Department of Heart and Lung Diseases, Sahlgrenska University Hospital, S-413 45 Gothenburg, Sweden

Per Björntorp
professor of medicine

Correspondence to:
R Rosmond
rolandrosmond@
hotmail.com

Endpiece
Different ways of saving lives

Because the doctors cared, and because one of them still believed in me when I believed in nothing, I have survived to tell the tale. It is not only the doctors who perform hazardous operations or give life-saving drugs in obvious emergencies who hold the scales at times between life and death. To sit quietly in a consulting room and talk to someone would not appear to the general public as a heroic or dramatic thing to do. In medicine there are many different ways of saving lives. This is one of them.

Coate M. *Beyond all reason.* London: Constable,1964.